Harris, A.
09/436347

-key terms

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     FILE 'REGISTRY' ENTERED AT 11:08:31 ON 01 FEB 2000
                E RITUXAN/CN 5
L1              1 S E3

     FILE 'CAPLUS' ENTERED AT 11:08:45 ON 01 FEB 2000
L1              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  RITUXAN/CN
L2          61809 SEA FILE=CAPLUS ABB=ON  PLU=ON  (HEMATOL? OR HAEMATOL?)(2
                  A)MALIGNAN? OR LEUKEM? OR LEUKAEM? OR (BPLL OR PLL OR
                  CLL)(S)(LEUKEM? OR LEUKAEM?)
L3           8709 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2(S)(TREAT? OR THERAP?)

L4              7 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND (ANTICD20 OR
                  ANTICD 20 OR ANTI(W)(CD20 OR CD 20) OR L1 OR RITUXAN)

L2          61809 SEA FILE=CAPLUS ABB=ON  PLU=ON  (HEMATOL? OR HAEMATOL?)(2
                  A)MALIGNAN? OR LEUKEM? OR LEUKAEM? OR (BPLL OR PLL OR
                  CLL)(S)(LEUKEM? OR LEUKAEM?)
L3           8709 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2(S)(TREAT? OR THERAP?)

L5              7 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND ((CHIMER?(5A)ANTIB
                  OD?)(5A)HUMAN?)

L6             14 L4 OR L5

=> d 1-14 .bevstr

L6   ANSWER 1 OF 14  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:         2000:65057  CAPLUS
TITLE:                    Antitumour activity of a chimeric antibody
                          against the leucocyte antigen CD48
AUTHOR(S):                Sun, Haiping; Biggs, James C.; Smith, Glenn M.
CORPORATE SOURCE:         CRC for Biopharmaceutical Research Ltd.,
                          Darlinghurst, 2010, Australia
SOURCE:                   Cancer Immunol. Immunother. (2000), 48(10),
                          595-602
                          CODEN: CIIMDN; ISSN: 0340-7004
PUBLISHER:                Springer-Verlag
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Preclin. studies with the murine anti-CD48 antibody, mHuLym3 (IgG2a)
     have shown it to be a potentially useful therapeutic
     reagent in the treatment of human leukemia and
     lymphoma.  For clin. use, humanised antibodies can have a no. of
     advantages over their original murine version, including mediation
     of higher effector cell function with human cells, longer serum
     half-life and lower immunogenicity.  In this study, we have produced
     a mouse/human chimeric HuLym3 antibody
     (cHuLym3) where the murine antibody const. regions have been
     replaced with human const. regions.  We report the prodn. and
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preclin. characterization of the antibody, cHuLym3, with potent in vitro and in vivo antitumor activity. The genes encoding the variable heavy and light chains were amplified by the polymerase chain reaction, sequenced and cloned into eukaryotic expression vectors contg. the human light- and heavy-chain const. regions (.kappa. and IgG1). The chimeric and murine HuLym3 antibodies had similar cell-binding specificity and affinity. In the human Raji cell severe combined immunodeficient mouse model the i.v. injection of cHuLym3 and mHuLym3 produced similar antitumor responses. Doses of cHuLym3 and mHuLym3 (100 .mu.g) on days 1, 2 and 4 after i.v. Raji cell injection produced a 40% longer time to hind-leg paralysis than when a control antibody was used. CHuLym3 had more potent activity than mHuLym3 in antibody-dependent cellular cytotoxicity (ADCC) assays in vitro, with human peripheral blood mononuclear cells as effectors. Up to 60% specific cell lysis was obsd. with cHuLym3 in ADCC assays. These properties suggest that anti-CD48 antibodies may be useful in the **treatment** of a no. of diseases including lymphoid **leukemias** and lymphoma.

L6 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:775057 CAPLUS
DOCUMENT NUMBER: 131:346017
TITLE: Chronic lymphocytic leukemia
AUTHOR(S): Keating, Michael J.
CORPORATE SOURCE: Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Semin. Oncol. (1999), 26(5, Suppl. 14), 107-114
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 65 refs. Research in chronic lymphocytic leukemia (CLL) has undergone a resurgence of interest in the last decade. While it is obvious that most patients with CLL have typical mature B cells, a no. of variants such as splenic lymphoma villous lymphocytes, mantle cell leukemia, and prolymphocytic leukemia need to be considered in the differential diagnosis. This can be established by immunophenotype studies and morphol. Cytogenetic abnormalities are emerging as being of interest, with abnormalities in chromosomes 11 and 17 having major prognostic significance. Immune dysregulation is complicated in that along with hypergamma-globulinemia and T-cell dysfunction, the emergence of antibodies directed against hematopoietic cells causes autoimmune hemolytic anemia, neutropenia, and thrombocytopenia. A no. of prognostic factors are emerging as being more influential in prognosis and stage, such as serum .beta.2-microglobulin and sol. CD23. Apoptosis dysregulation is a major feature of CLL, and while no clear pattern has emerged, abnormal levels of bcl2 are common in CLL and bcl2 to bax ratios are also commonly disturbed. Bcl1 levels

are commonly increased. Treatment has changed radically. The purine analogs have been demonstrated to be the most active group of drugs in CLL. Combinations of purine analogs, such a fludarabine or 2-chloro-deoxyadenosine, with alkylating agents are emerging as new treatments. The most recent development has been the emergence of two monoclonal antibodies, rituximab (**Rituxan**; IDEC Pharmaceuticals, San Diego, CA, and Genentech, Inc, San Francisco, CA; directed against CD20) and Campath-1H (directed against CD52 in CLL). The activity of rituximab in lymphoma has been less prominent in small lymphocytic lymphoma (the lymphomatous counterpart of CLL) and this has led to dose escalation studies in CLL with a good level of response. Campath-1H is emerging as another major antibody with marked effect against disease, particularly in the blood and bone marrow. Autologous, allogeneic, and mini-transplant are also being explored extensively. The prognosis for patients with CLL is changing as these new treatments become available.

L6 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:644119 CAPLUS
DOCUMENT NUMBER: 131:241735
TITLE: Cytokine-release syndrome in patients with B-cell chronic lymphocytic **leukemia** and high lymphocyte counts after **treatment** with an **anti-CD20** monoclonal antibody (rituximab, IDEC-C2B8)
AUTHOR(S): Winkler, U.; Jensen, M.; Manzke, O.; Schulz, H.; Diehl, V.; Engert, A.
CORPORATE SOURCE: Department I of Internal Medicine, University of Cologne, Cologne, Cologne, D-50924, Germany
SOURCE: Blood (1999), 94(7), 2217-2224
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Eleven patients with relapsed fludarabine-resistant B-cell chronic lymphocytic **leukemia** (**CLL**) or **leukemic** variants of low-grade B-cell non-Hodgkin's lymphoma (NHL) were **treated** with the chimeric monoclonal **anti-CD20** antibody rituximab (IDEC-C2B8). Peripheral lymphocyte counts at baseline varied from 0.2 to 294.3.times.109/L. During the first rituximab infusion, patients with lymphocyte counts exceeding 50.0.times.109/L experienced a severe cytokine-release syndrome. Ninety minutes after onset of the infusion, serum levels of tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-6 (IL-6) peaked in all patients. Elevated cytokine levels during treatment were assocd. with clin. symptoms, including fever, chills, nausea, vomiting, hypotension, and dyspnea. Lymphocyte and platelet counts dropped to 50% to 75% of baseline values within 12 h after the onset

of the infusion. Simultaneously, there was a 5-fold to 10-fold increase of liver enzymes, d-dimers, and lactate dehydrogenase (LDH), as well as a prolongation of the prothrombin time. Frequency and severity of first-dose adverse events were dependent on the no. of circulating tumor cells at baseline: patients with lymphocyte counts greater than 50.0.times.109/L experienced significantly more adverse events of National Cancer Institute (NCI) grade III/IV toxicity than patients with less than 50.0.times.109/L peripheral tumor cells (P =.0017). Due to massive side effects in the first patient treated with 375 mg/m2 in 1 day, a fractionated dosing schedule was used in all subsequent patients with application of 50 mg rituximab on day 1,150 mg on day 2, and the rest of the 375 mg/m2 dose on day 3. While the patient with the **leukemic** variant of the mantle-cell NHL achieved a complete remission (9 mo+) after **treatment** with 4.times.375 mg/m2 rituximab, efficacy in patients with relapsed fludarabine-resistant B-**CLL** was poor: 1 partial remission, 7 cases of stable disease, and 1 progressive disease were obsd. in 9 evaluable patients with **CLL**. On the basis of these data, different infusion schedules and/or combination regimens with chemotherapeutic drugs to reduce tumor burden before treatment with rituximab will have to be evaluated.

IT **174722-31-7**, Rituximab
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cytokine-release syndrome in humans with B-cell chronic lymphocytic **leukemia** and high lymphocyte counts after **treatment** with rituximab)

L6 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:504937 CAPLUS
DOCUMENT NUMBER: 131:153487
TITLE: Minimal residual disease in patients with hairy cell **leukemia** in complete remission **treated** with 2-chlorodeoxyadenosine or 2'-deoxycoformycin and prediction of early relapse
AUTHOR(S): Tallman, Martin S.; Hakimian, David; Kopecky, Kenneth J.; Wheaton, Susan; Wollins, Eric; Foucar, Kathy; Cassileth, Peter A.; Habermann, Thomas; Grever, Michael; Rowe, Jacob M.; Peterson, LoAnn C.
CORPORATE SOURCE: Northwestern University Medical School, Chicago, IL, 60611, USA
SOURCE: Clin. Cancer Res. (1999), 5(7), 1665-1670
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purine nucleoside analogs 2-chlorodeoxyadenosine (2-CdA) and 2'-deoxycoformycin (2'-DCF) induce complete remission (CR) in the majority of patients with hairy cell leukemia. However, minimal residual disease (MRD) has been detected in bone marrow core biopsies using immunohistochem. techniques in patients achieving CR by conventional criteria. This study was designed to compare the prevalence of MRD with each agent in patients in CR by using conventional criteria and the relapse-free survival for patients with and without MRD. Bone marrow biopsies from 39 patients treated with a single cycle of 2-CdA and 27 patients treated with multiple cycles of 2'-DCF were studied. The monoclonal antibodies **anti-CD20**, DBA.44, and anti-CD45RO were used to evaluate the paraffin-embedded bone marrow core biopsies for MRD. Five of 39 patients (13%) treated with 2-CdA had MRD, as compared to 7 of 27 patients (26%) treated with 2'-DCF (two-tailed P = 0.21). Relapse has occurred in two of the five patients with MRD after 2-CdA treatment and in four of the seven patients with MRD after 2'-DCF treatment. In total, 6 of the 12 patients (50%) with MRD have relapsed, whereas 3 of 54 patients (6%) without MRD have relapsed, and 2 patients have died without evidence of relapse. The estd. 4-yr relapse-free survival among patients with MRD is 55% (.+-. 15%, SE), compared to 88% (.+-. 5%, SE) among patients without MRD (two-tailed P = 0.0023). The prevalence of MRD detected in a subset of patients in CR after either 2-CdA or 2'-DCF treatment did not differ significantly. However, the presence of MRD is assocd. with an increased risk of relapse.

L6 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:195380 CAPLUS

DOCUMENT NUMBER: 130:336689

TITLE: Rituximab **therapy** in **hematologic malignancy** patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance

AUTHOR(S): Byrd, John C.; Waselenko, Jamie K.; Maneatis, Thomas J.; Murphy, Timothy; Ward, Frank T.; Monahan, Brian P.; Sipe, Melissa A.; Donegan, Sarah; White, Christine A.

CORPORATE SOURCE: Division of Hematology-Oncology, Walter Reed Army Medical Center, Washington, DC, 20307, USA

SOURCE: J. Clin. Oncol. (1999), 17(3), 791-795
CODEN: JCONDN; ISSN: 0732-183X

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: Rituximab was recently approved for use in relapsed, low-grade non-Hodgkin's lymphoma; however, few data exist regarding

the safety of this agent in patients with a high no. of tumor cells in the blood. Methods and Results: After the observation at our institution of a rapid redn. of peripheral-blood tumor cells with assocd. severe pulmonary infusion-related toxicity in two patients with refractory **hematol. malignancies**, data on three addnl. cases were collected from physician-submitted reports of adverse events related to rituximab **treatment**. Five patients with **hematol. malignancies** possessing a high no. of blood tumor cells were **treated** with rituximab and developed rapid tumor clearance. The median age was 68 yr (range, 26 to 78 yr). Patients were diagnosed with B-cell pro-lymphocytic leukemia (n = 2), chronic lymphocytic leukemia (n = 2), or transformed non-Hodgkin's lymphoma (n = 1). All of these patients had bulky adenopathy or organomegaly. All five patients developed a unique syndrome of severe infusion-related reactions, thrombocytopenia, rapid decrement in circulating tumor cell load, and mild electrolyte evidence of tumor lysis, and all required hospitalization. In addn., one patient developed ascites. These events resolved, and four patients were subsequently treated with rituximab without significant complications. Conclusion: Rituximab administration in patients who have a high no. of tumor cells in the blood may have an increased likelihood of severe initial infusion-related reactions. These data also suggest that rituximab may have activity in a variety of other lymphoid neoplasms, such as chronic lymphocytic leukemia and B-cell pro-lymphocytic leukemia.

IT **174722-31-7**, Rituximab
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rituximab **therapy** in **hematol. malignancy** patients with circulating blood tumor cells: assocn. with increased infusion-related side effects and rapid blood tumor clearance)

L6 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:761814 CAPLUS
DOCUMENT NUMBER: 130:24110
TITLE: Human tumor necrosis factor receptor-like 2 (TR2) antibodies
INVENTOR(S): Harrop, Jeremy A.; Holmes, Stephen D.; Reddy, Manjula P.; Truneh, Alemseged
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Smithkline Beecham PLC
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9851346	A1	19981119	WO 1998-US9744	19980512

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1997-46249 19970512

AB Antibodies to novel members of the Tumor Necrosis Factor (TNF) receptor family called TR2 and their uses in pathol. conditions are described. Hybridoma cell lines producing such mAbs, methods of in vivo imaging of pathol. conditions, and methods of treating and diagnosing pathol. conditions caused by abnormal functioning, prodn., or metab. of TR2 receptors are also provided. In vitro assays for detecting the presence of TR2 and for evaluating the binding affinity of a test compd. are also described. The antibodies or monoclonal antibodies are useful for diagnosing systemic lupus erythematosus, idiopathic thrombocytopenic purpura, rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease, insulin-dependent diabetes mellitus, allergic disorders, asthma, allergic rhinitis, atopic dermatitis, cancer, lymphomas, leukemias, viral infections, and AIDS. TR2-Ig fusion protein was prepd. and purified, and purified recombinant TR2 was used for raising monoclonal antibodies and hybridomas for the disclosed purpose.

L6 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:661515 CAPLUS
DOCUMENT NUMBER: 129:274703
TITLE: Immunotherapy of B-cell malignancies using anti-CD22 antibodies
INVENTOR(S): Goldenberg, David M.
PATENT ASSIGNEE(S): IMMUNOMEDICS, INC., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9842378	A1	19981001	WO 1998-US5075	19980317

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9867610	A1	19981020	AU 1998-67610	19980317
EP 969866	A1	20000112	EP 1998-912936	19980317

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.:	US 1997-41506	19970324
	WO 1998-US5075	19980317

AB B-Cell malignancies, such as the B-cell subtype of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, are significant contributors to cancer mortality. The response of B-cell malignancies to various forms of treatment is mixed. Traditional methods of treating B-cell malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. Immunotherapy with **anti-CD20** antibodies have also provided limited success. The use of antibodies that bind with the CD22 antigen, however, provides an effective means to **treat** B-cell malignancies such as indolent and aggressive forms of B-cell lymphomas, and acute and chronic forms of lymphatic **leukemias**. Moreover, immunotherapy with anti-CD22 antibodies requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies. Immunoconjugates comprising anti-CD22 antibody and radioisotope or cytokine, and combination treatment with chemotherapeutic agent are also disclosed.

L6 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1997:290112 CAPLUS
DOCUMENT NUMBER:	126:263167
TITLE:	Recombinant anti-CD4 antibodies for human therapy
INVENTOR(S):	Hanna, Nabil; Newman, Roland A.; Reff, Mitchell E.
PATENT ASSIGNEE(S):	Idec Pharmaceuticals Corporation, USA
SOURCE:	PCT Int. Appl., 154 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9709351	A1	19970313	WO 1996-US14324	19960905

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ,

VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA

CA 2231182	AA	19970313	CA 1996-2231182	19960905
AU 9669162	A1	19970327	AU 1996-69162	19960905
EP 854885	A1	19980729	EP 1996-929936	19960905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1200737	A	19981202	CN 1996-197943	19960905
BR 9610404	A	19990706	BR 1996-10404	19960905
JP 11514216	T2	19991207	JP 1996-511411	19960905
NO 9800915	A	19980506	NO 1998-915	19980303
PRIORITY APPLN. INFO.:			US 1995-523894	19950906
			WO 1996-US14324	19960905

AB **Chimeric antibodies** specific to **human** CD4 antigen, DNA encoding, pharmaceutical compns. contg. them and use thereof as therapeutic agents are taught. These chimeric antibodies contain Old World monkey variable sequences and human const. domain sequences, preferably human .gamma. 1, .gamma. 4 or mutated forms thereof. These antibodies possess desirable therapeutic properties including low antigenicity, reduced (or absent) T cell depleting activity, good affinity to human CD4 and enhanced stability (in vivo half-life). These antibodies are useful for **treating** autoimmune disease such as rheumatoid arthritis and nonautoimmune disease such as **leukemia**, lymphoma, graft-vs.-host disease, asthma, transplant rejection, and HIV infection. SupT1 cell-derived CD4 was used as immunogen to raise anti-CD4 IgG1 CE9.1-producing immortalized B cell line from cynomolgus monkey. Macaque/human chimeric anti-CD4 IgG4 CE9.gamma.4PE was prepd. by genetic engineering.

L6 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:588743 CAPLUS
DOCUMENT NUMBER: 125:212708
TITLE: Receptor fusion proteins and chimeric genes encoding them and their use in the control of proliferation in the treatment of disease
INVENTOR(S): Capon, Daniel J.; Tian, Huan; Smith, Douglas H.; Winslow, Genine A.; Siekevitz, Miriam
PATENT ASSIGNEE(S): Cell Genesys, Inc., USA
SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9623881	A1	19960808	WO 1996-US1292	19960202
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AZ, BY, KG, KZ				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5741899	A	19980421	US 1995-481003	19950607
US 5837544	A	19981117	US 1995-485293	19950607
CA 2221634	AA	19960808	CA 1996-2221634	19960202
AU 9648612	A1	19960821	AU 1996-48612	19960202
EP 821730	A1	19980204	EP 1996-904532	19960202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
PRIORITY APPLN. INFO.:			US 1995-382846	19950202
			WO 1996-US1292	19960202

AB Chimeric receptors for proliferation-stimulating effectors are described for use in the treatment of disease (cancer, infectious, or autoimmune disease). The receptors are made up of combinations of domains from known receptors. One group has an extracellular clustering domain (ECD), transmembrane domain (TM), proliferation signaling domain (PSD) that can signal a host cell to divide. A second group has an intracellular clustering domain (ICD) and a proliferation signaling domain (PSD) that can signal a host cell to divide. A third group has an extracellular clustering domain (ECD) or an intracellular clustering domain (ICD), a transmembrane domain (TM), proliferation signaling domain (PSD), and an effector signaling domain that can signal an effector function and a host cell to divide. Chimeric genes for these receptors and methods for their expression and the therapeutic uses of the receptors and genes are described. The prepn. of fusion proteins of the ligand receptor and extracellular clustering domains of CD4 and Janus kinase or cytokine receptor subunits are described.

L6 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1996:340661 CAPLUS
DOCUMENT NUMBER:	125:8478
TITLE:	Immunoconjugates and humanized antibodies specific for B-cell lymphoma and leukemia cells
INVENTOR(S):	Leung, Shuion; Hansen, Hans
PATENT ASSIGNEE(S):	Immunomedics, Inc., USA
SOURCE:	PCT Int. Appl., 66 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604925	A1	19960222	WO 1995-US9641	19950811
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2195557	AA	19960222	CA 1995-2195557	19950811
AU 9532726	A1	19960307	AU 1995-32726	19950811
EP 771208	A1	19970507	EP 1995-929338	19950811
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL				
JP 10505231	T2	19980526	JP 1995-507371	19950811
US 5789554	A	19980804	US 1996-690102	19960731
PRIORITY APPLN. INFO.:			US 1994-289576	19940812
			WO 1995-US9641	19950811

AB **Chimeric** and **humanized** LL2 monoclonal **antibody**, isolated DNAs encoding these antibodies, vectors contg. the DNA and conjugates of **chimeric** and **humanized chimeric** LL2 **antibodies** with cytotoxic agents or labels for use in **therapy** and diagnosis of B-cell lymphomas and **leukemias**. Demonstrated in examples were choice of human frameworks and sequence design for the humanization of LL2 monoclonal antibody, PCR cloning and sequence elucidation for LL2 heavy and light chain variable regions, PCR/gene synthesis of the humanized V genes, construction and expression and purifn. of chimeric LL2 antibodies, etc.

L6 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1996:105496 CAPLUS
DOCUMENT NUMBER:	124:249901
TITLE:	Minimal residual disease may predict bone marrow relapse in patients with hairy cell **leukemia treated** with 2-chlorodeoxyadenosine
AUTHOR(S):	Wheaton, Susan; Tallman, Martin S.; Hakimian, David; Peterson, LoAnn
CORPORATE SOURCE:	Dep. of Pathology, Northwestern Univ. Medical School, Chicago, IL, USA
SOURCE:	Blood (1996), 87(4), 1556-60 CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Minimal residual disease (MRD) can be detected in bone marrow core biopsies of patients with hairy cell **leukemia** (HCL) after **treatment** with 2-chlorodeoxyadenosine (2-CdA) using immunohistochem. (IHC) techniques. The purpose of this study was to

det. whether the presence of MRD predicts bone marrow relapse. We studied paraffin-embedded bone marrow core biopsies from 39 patients with HCL in complete remission (CR) 3 mo after a single cycle of 2-CdA. Biopsies performed 3 mo posttherapy and annually thereafter were examd. by routine hematoxylin and eosin (H&E) staining and IHC using the monoclonal antibodies (MoAbs) anti-CD45RO, **anti-CD20**, and DBA.44. At 3 mo after therapy, 5 of 39 (13%) patients had MRD detectable by IHC that was not evident by routine H&E staining. Two of the five patients (40%) with MRD at 3 mo have relapsed, whereas only 2 of 27 (7%) patients with no MRD and at least 1 yr of follow up relapsed (P = .11). Over the 3-yr follow-up period, two addnl. patients developed MRD. Overall, three of six (50%) patients with MRD detected at any time after therapy have relapsed, whereas only 1 of 25 (4%) patients without MRD has relapsed (P = .016). There data suggest that the presence of MRD after treatment with 2-CdA may predict relapse.

L6 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:57767 CAPLUS
DOCUMENT NUMBER: 118:57767
TITLE: Biological and immunological features of humanized M195 (anti-CD33) monoclonal antibodies
AUTHOR(S): Caron, Philip C.; Co, Man Sung; Bull, Marcia K.; Avdalovic, Nevenka M.; Queen, Cary; Scheinberg, David A.
CORPORATE SOURCE: Mem. Sloan-Kettering Cancer Cent., New York, NY, 10021, USA
SOURCE: Cancer Res. (1992), 52(24), 6761-7
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human-mouse chimeric IgG1 and IgG3 (ChG1, ChG3) and complementarity-detg. region-grafted, humanized IgG1 and IgG3 (HuG1, HuG3) constructs of the mouse monoclonal antibody (mAb) M195 were characterized. M195 is a murine IgG2a, anti-CD33 mAb, specifically reactive with acute myelogenous leukemia cells, that is active as an antileukemia agent in humans. The new mAb constructs maintained specificity and biol. function, including rapid internalization after binding to the cell surface, which has been important for delivery of therapeutic isotopes in patients. Although previously reported complementarity-detg. region-grafted mAbs had reduced avidities, the HuG1 and HuG3 M195 showed up to an 8.6- and 4-fold higher binding avidity, resp., than the original murine mAb. All constructs were effective at mediating rabbit complement-mediated cytotoxicity against HL60 targets. Fibroblasts transfected with CD33 genes and expressing high levels of CD33 antigen were also lysed in the presence of human complement, but HL60 cells or fibroblasts with lower CD33 levels were not killed. Thus, the inability of M195 and constructs to kill HL60 targets with human

complement is due to the much lower antigen d. on HL60 cells compared to CD33+ fibroblasts. Unlike the murine M195, the **chimeric** and **humanized** M195 demonstrated **antibody**-dependent cell-mediated cytotoxicity using **human** peripheral blood mononuclear cells as effectors. Because the chimeric and humanized M195 have improved avidities as compared to the original M195 and have, in addn., the potential to avoid human anti-mouse antibody responses and to recruit human effector functions, these new constructs may be useful **therapeutically**, either alone or conjugated to toxins or isotopes, in the **treatment** of acute myelogenous **leukemia**.

L6 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:649900 CAPLUS
DOCUMENT NUMBER: 117:249900
TITLE: Monoclonal antibodies to stem cell factor (SCF) receptors
INVENTOR(S): Lin, Nancy; Broudy, Virginia C.
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9217505	A1	19921015	WO 1992-US2674	19920403
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
EP 578774	A1	19940119	EP 1992-910836	19920403
EP 578774	B1	19980729		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 06506833	T2	19940804	JP 1992-510017	19920403
AT 169031	E	19980815	AT 1992-910836	19920403
ES 2118820	T3	19981001	ES 1992-910836	19920403
US 5489516	A	19960206	US 1993-11078	19930129
US 5922847	A	19990713	US 1994-255193	19940607
US 5906938	A	19990525	US 1995-449139	19950524
US 5919911	A	19990706	US 1995-462638	19950605
PRIORITY APPLN. INFO.:			US 1991-681245	19910405
			WO 1992-US2674	19920403
			US 1993-11078	19930129

AB A monoclonal antibody (SR-1) to the human SCF receptor (identified as proto-oncogene c-kit) of hematopoietic precursor cells binds to the receptor and inhibits binding of SCF to the receptor. Hematopoietic cells are sepd. from other cells, for use in bone

marrow transplantation, by utilizing their affinity for the above antibody in column chromatog., fluorescence-activated cell sorting, or immune adherence methods. **Leukemia** and solid tumors are **treated** by administration of SR-1 or a binding fragment thereof conjugated to an appropriate antineoplastic agent. Thus, mice were immunized with OCIM1 human erythroleukemia cells bearing SCF receptors for prodn. of spleen-myeloma hybrid cells by fusion; genomic DNA from the hybridomas was used to produce **chimeric** monoclonal **antibodies** having murine variable regions and **human** const. regions by recombinant DNA techniques.

L6 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1989:33411 CAPLUS
DOCUMENT NUMBER: 110:33411
TITLE: Anti-CD19 immunotoxins for in vivo immunotherapy of B-lineage acute lymphoblastic leukemias
AUTHOR(S): Uckun, Fatih M.
CORPORATE SOURCE: Health Sci. Cent., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Antibody, Immunoconjugates, Radiopharm. (1988), 1(3), 247-62
CODEN: AIRAEB; ISSN: 0892-7049
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Monoclonal antibodies against B-lymphoblasts leukemia specific antigen CD-19 (anti-CD19) were linked to pokeweed antiviral protein (PAP), recombinant ricin A chain, saporin, and momordin. The in vivo and ex vivo antileukemic activity of the resulting immunotoxin conjugates was compared to that of conjugates composed of **anti-CD20** and anti-CD22 antibodies linked to PAP, anti-CD24 and anti-CD9 and anti-CD10 linked to complement C' or 4-hydroxyperoxycyclophosphamide. The active immunotoxins are promising agents for **leukemia treatment** and for ex vivo purging of **leukemic** cells from bone marrow transplants.

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, SCISEARCH, JICST-EPLUS, CANCERLIT, TOXLIT, TOXLINE' ENTERED AT 11:28:09 ON 01 FEB 2000)
L7 148 S L6
L8 71 DUP REM L7 (77 DUPLICATES REMOVED)
L9 31 S L7 AND ADMIN?
L10 17 DUP REM L9 (14 DUPLICATES REMOVED)

L10 ANSWER 1 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999367285 EMBASE
TITLE: Strategies for developing effective radioimmunotherapy for solid tumors.
AUTHOR: DeNardo G.L.; O'Donnell R.T.; Kroger L.A.; Richman

C.M.; Goldstein D.S.; Shen S.; DeNardo S.J.
CORPORATE SOURCE: G.L. DeNardo, Sec. of Radiodiagnosis and Therapy, Univ. of California Davis Med. Ctr., 1508 Alhambra Boulevard, Sacramento, CA 95816, United States
SOURCE: Clinical Cancer Research, (1999) 5/10 SUPPL. (3219s-3223s).
Refs: 33
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Single-agent radioimmunotherapy (RIT) has proven efficacy as a **treatment** for **hematological malignancies**, particularly non-Hodgkin's lymphoma. Although promising, RIT has been less effective for solid tumors, in part because they are less radiosensitive. Bone marrow transplantation permits the **administration** of larger radiopharmaceutical doses, but the results of bone marrow transplantation-supported RIT for solid tumors have been marginal. The purpose of this publication is to provide an overview of promising RIT strategies for solid tumors. It is apparent that combination **therapy** is required, but optimization of the radiopharmaceutical should be the first step. Metallic radionuclides provide higher tumor radiation doses but not necessarily an improved **therapeutic** index, that is, the ratio of tumor:normal tissue radiation doses. Biodegradable peptide linkers between the chelated metal and the antibody improve the **therapeutic** index. Further improvements depend on identification of synergistic **therapies** which recognize that: (a) continuous, low-dose radionuclide **therapy** acts through apoptosis; and (b) apoptosis is often blocked because most tumors have ineffective p53 and increased Bcl-2. Taxanes are particularly attractive as synergistic agents for RIT because they induce cell cycle arrest in the radiosensitive G2-M phase and p53-independent apoptosis. Optimal sequence and timing for combined modality RIT are critical to achieve synergy. Data from preclinical and clinical studies will be reviewed to illustrate the potential of these strategies.

L10 ANSWER 2 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999346611 EMBASE
TITLE: Cytokine-release syndrome in patients with B-cell chronic lymphocytic **leukemia** and high lymphocyte counts after **treatment** with an **anti-CD20** monoclonal antibody

(rituximab, IDEC-C2B8).

AUTHOR: Winkler U.; Jensen M.; Manzke O.; Schulz H.; Diehl V.; Engert A.

CORPORATE SOURCE: Dr. A. Engert, Department I of Internal Medicine, University of Cologne, Joseph-Stelzmann-Str. 9, D-50927 Cologne, Germany.
sabine.kluge@medizin.unikoeln.de

SOURCE: Blood, (1 Oct 1999) 94/7 (2217-2224).
Refs: 23
ISSN: 0006-4971 CODEN: BLOOAW

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Eleven patients with relapsed fludarabine-resistant B-cell chronic lymphocytic **leukemia** (**CLL**) or **leukemic** variants of low-grade B-cell non- Hodgkin's lymphoma (NHL) were **treated** with the chimeric monoclonal **anti-CD20** antibody rituximab (IDEC-C2B8). Peripheral lymphocyte counts at baseline varied from 0.2 to 294.3 x 109/L. During the first rituximab infusion, patients with lymphocyte counts exceeding 50.0 x 109/L experienced a severe cytokine-release syndrome. Ninety minutes after onset of the infusion, serum levels of tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-6 (IL-6) peaked in all patients. Elevated cytokine levels during **treatment** were associated with clinical symptoms, including fever, chills, nausea, vomiting, hypotension, and dyspnea. Lymphocyte and platelet counts dropped to 50% to 75% of baseline values within 12 hours after the onset of the infusion. Simultaneously, there was a 5-fold to 10-fold increase of liver enzymes, d- dimers, and lactate dehydrogenase (LDH), as well as a prolongation of the prothrombin time. Frequency and severity of first-dose adverse events were dependent on the number of circulating tumor cells at baseline: patients with lymphocyte counts greater than 50.0 x 109/L experienced significantly more adverse events of National Cancer Institute (NCI) grade III/IV toxicity than patients with less than 50.0 x 109/L peripheral tumor cells (P = .0017). Due to massive side effects in the first patient **treated** with 375 mg/m2 in 1 day, a fractionated dosing schedule was used in all subsequent patients with application of 50 mg rituximab on day 1, 150 mg on day 2, and the rest of the 375 mg/m2 dose on day 3. While the patient with the **leukemic** variant of the mantle-cell NHL achieved a complete remission (9 months+) after **treatment** with 4 x 375 mg/m2 rituximab, efficacy in patients with relapsed fludarabine-resistant

B-**CLL** was poor: 1 partial remission, 7 cases of stable disease; and 1 progressive disease were observed in 9 evaluable patients with **CLL**. On the basis of these data, different infusion schedules and/or combination regimens with chemotherapeutic drugs to reduce tumor burden before **treatment** with rituximab will have to be evaluated.

L10 ANSWER 3 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999251254 EMBASE
TITLE: Minimal residual disease in patients with hairy cell **leukemia** in complete remission **treated** with 2-chlorodeoxyadenosine or 2'-deoxycoformycin and prediction of early relapse.
AUTHOR: Tallman M.S.; Hakimian D.; Kopecky K.J.; Wheaton S.; Wollins E.; Foucar K.; Cassileth P.A.; Habermann T.; Grever M.; Rowe J.M.; Peterson L.C.
CORPORATE SOURCE: M.S. Tallman, Division of Hematology/Oncology, Department of Medicine, Northwestern Univ. Medical School, 233 East Erie Street, Chicago, IL 60611, United States
SOURCE: Clinical Cancer Research, (1999) 5/7 (1665-1670). Refs: 34
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The purine nucleoside analogues 2-chlorodeoxyadenosine (2-CdA) and 2'- deoxycoformycin (2'-DCF) induce complete remission (CR) in the majority of patients with hairy cell **leukemia**. However, minimal residual disease (MRD) has been detected in bone marrow core biopsies using immunohistochemical techniques in patients achieving CR by conventional criteria. This study was designed to compare the prevalence of MRD with each agent in patients in CR by using conventional criteria and the relapse-free survival for patients with and without MRD. Bone marrow biopsies from 39 patients **treated** with a single cycle of 2-CdA and 27 patients **treated** with multiple cycles of 2'-DCF were studied. The monoclonal antibodies **anti-CD20**, DBA.44, and anti-CD45RO were used to evaluate the paraffin-embedded bone marrow core biopsies for MRD. Five of 39 patients (13%) **treated** with 2-CdA had MRD, as compared to 7 of 27 patients (26%) **treated** with 2'-DCF (two-tailed P = 0.21). Relapse has occurred in two of the five patients with MRD after 2-CdA **treatment** and in four of the seven patients with MRD after 2'-DCF **treatment**. In total, 6 of the 12 patients (50%)

with MRD have relapsed, whereas 3 of 54 patients (6%) without MRD have relapsed, and 2 patients have died without evidence of relapse. The estimated 4-year relapse-free survival among patients with MRD is 55% (.+-. 15%, SE), compared to 88% (.+-. 5%, SE) among patients without MRD (two-tailed P = 0.0023). The prevalence of MRD detected in a subset of patients in CR after either 2-CdA or 2'-DCF **treatment** did not differ significantly. However, the presence of MRD is associated with an increased risk of relapse.

L10 ANSWER 4 OF 17 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 1999:628954 SCISEARCH
THE GENUINE ARTICLE: 224MF
TITLE: Factors affecting I-131-Lym-1 pharmacokinetics and radiation dosimetry in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia
AUTHOR: DeNardo G L (Reprint); DeNardo S J; Shen S; DeNardo D A; Mirick G R; Macey D J; Lamborn K R
CORPORATE SOURCE: MOL CANC INST, 1508 ALHAMBRA BLVD, RM 3100, SACRAMENTO, CA 95816 (Reprint); UNIV CALIF DAVIS, MED CTR, SACRAMENTO, CA 95817; UNIV CALIF SAN FRANCISCO, SAN FRANCISCO, CA 94143; UNIV ALABAMA, BIRMINGHAM, AL
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (AUG 1999) Vol. 40, No. 8, pp. 1317-1326.
Publisher: SOC NUCLEAR MEDICINE INC, 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316.
ISSN: 0161-5505.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Lym-1, a monoclonal antibody that preferentially targets malignant lymphocytes, has induced **therapeutic** responses in patients with non-Hodgkin's lymphoma (NHL) and chronic lymphocytic **leukemia** (**CLL**) when labeled with I-131. Responders had statistically significant prolongation of survival compared with nonresponders. The nonmyeloablative, maximum tolerated dose for each of two doses of I-131-Lym-1 was 3.7 G89/m(2) (total 7.4 GBq/m(2) [100 mCi/m(2), total 200 mCi/m(2)]) of body surface area. The purpose of this study was to determine the pharmacokinetics and radiation dosimetry for the initial I-131-Lym-1 **therapy** dose in patients with NHL and **CLL** and to compare tumor dosimetry with I-131-Lym-1 dosing and other patient parameters. Methods: Fifty-one patients with stage 3 or 4 lymphoma were **treated** with I-131-Lym-1 (0.74-8.04 GBq [20-217 mCi]) in either a maximum tolerated dose (MTD) or low-dose (LD) trial. Total Lym-1 given to each patient was sufficient in all instances to

exceed the threshold required for stable pharmacokinetics. Quantitative imaging and physical examination, including caliper and CT measurement of tumor size and analysis of blood, urine and feces, were performed for a period of 7 to 10 d after infusion to assess pharmacokinetics and radiation dosimetry. Clinical records were reviewed to obtain data required for comparative assessments. Results: The concentration (%ID/g) and biologic half-time of I-131-lym-1 in tumor were about twice those in normal tissues, although tumor half-time was similar to that of the thyroid. Pharmacokinetics were similar for patients in the MTD and LD trials, and for NHL and **CLL** patients in the LD trial, except that the latter group had less tumor concentration of I-131. Mean tumor radiation dose per unit of **administered** I-131 was 1.0 Gy/GBq (3.7 rad/mCi) for patients with NHL whether in MTD or LD trials, about nine times greater than that for body or marrow. Tumor radiation dose was less and liver radiation dose was more in patients with **CLL**. Otherwise, radiation dosimetry was, on average, remarkably similar among groups of patients and among individual patients. Pharmacokinetics and dosimetry did not appear to be influenced by the amount of I-131 or Lym-1 within the ranges **administered**. Tumor concentration of I-131 and radiation dose per gigabecquerel were inversely related to tumor size but did not seem to be related to histologic grade or type, tumor burden or **therapeutic** response. Conclusion: The **therapeutic** index of I-131-Lym-1 was favorable, although the index for patients with **CLL** was less than that for patients with NHL. Pharmacokinetics and radiation dosimetry were, on average, remarkably similar among patients and groups of patients in different trials.

L10 ANSWER 5 OF 17 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 1999:178837 BIOSIS
DOCUMENT NUMBER: PREV199900178837
TITLE: Rituximab **therapy** in **hematologic malignancy** patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance.
AUTHOR(S): Byrd, John C. (1); Waselenko, Jamie K.; Maneatis, Thomas J.; Murphy, Timothy; Ward, Frank T.; Monahan, Brian P.; Sipe, Melissa A.; Donegan, Sarah; White, Christine A.
CORPORATE SOURCE: (1) Clinical Research, Hematology Oncology Service, Walter Reed Army Medical Center, 6900 Georgia Ave, NW, Ward 78, Washington, DC, 20307 USA
SOURCE: Journal of Clinical Oncology, (March, 1999) Vol. 17, No. 3, pp. 791-795.
ISSN: 0732-183X.
DOCUMENT TYPE: Article

LANGUAGE: English

AB Purpose: Rituximab was recently approved for use in relapsed, low-grade non-Hodgkin's lymphoma; however, few data exist regarding the safety of this agent in patients with a high number of tumor cells in the blood. Methods and Results: After the observation at our institution of a rapid reduction of peripheral-blood tumor cells with associated severe pulmonary infusion-related toxicity in two patients with refractory **hematologic malignancies**, data on three additional cases were collected from physician-submitted reports of adverse events related to rituximab **treatment**. Five patients with **hematologic malignancies** possessing a high number of blood tumor cells were **treated** with rituximab and developed rapid tumor clearance. The median age was 68 years (range, 26 to 78 years). Patients were diagnosed with B-cell prolymphocytic **leukemia** (n = 2), chronic lymphocytic **leukemia** (n = 2), or transformed non-Hodgkin's lymphoma (n = 1). All of these patients had bulky adenopathy or organomegaly. All five patients developed a unique syndrome of severe infusion-related reactions, thrombocytopenia, rapid decrement in circulating tumor cell load, and mild electrolyte evidence of tumor lysis, and all required hospitalization. In addition, one patient developed ascites. These events resolved, and four patients were subsequently **treated** with rituximab without significant complications. Conclusion: Rituximab **administration** in patients who have a high number of tumor cells in the blood may have an increased likelihood of severe initial infusion-related reactions. These data also suggest that rituximab may have activity in a variety of other lymphoid neoplasms, such as chronic lymphocytic **leukemia** and B-cell prolymphocytic **leukemia**.

L10 ANSWER 6 OF 17 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999368224 MEDLINE
DOCUMENT NUMBER: 99368224
TITLE: S-phase induction by interleukin-6 followed by chemotherapy in patients with chronic lymphocytic leukemia and non-Hodgkin's lymphoma.
AUTHOR: Brown P D; Diamant M; Jensen P O; Geisler C H; Mortensen B T; Nissen N I
CORPORATE SOURCE: Department of Hematology, Rigshospitalet, Copenhagen, Denmark.
SOURCE: LEUKEMIA AND LYMPHOMA, (1999 Jul) 34 (3-4) 325-33. Journal code: BNQ. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY WEEK: 19991105

AB Interleukin-6 (IL-6) has in vitro demonstrated growth regulatory effects on tumor cells from patients with chronic lymphocytic **leukemia** (**CLL**) and lymphoma. The proliferation rate of these cells is usually very low and this is thought to be one of the reasons for the lack of a curative potential of cytostatic chemotherapy in **CLL** and low grade NHL. Recombinant human (rh) IL-6 might increase the in vivo proliferation rate leading to a higher sensitivity for chemotherapy. We tested this hypothesis by **administering** rhIL-6 to 9 **CLL** patients and 3 NHL patients in doses of 2.5 micrograms/kg, 5 micrograms/kg and 10 micrograms/kg s.c. daily for 5 days followed by CHOP chemotherapy on the last day of rhIL-6 injection. Six patients had two **treatment** cycles. The proportion of cells in S-phase was determined by the bromodeoxyuridine labeling index (LI). Three patients achieved a partial remission, one patient had progressive disease and the remaining patients demonstrated no change. Two patients, who received 10 micrograms/kg/day rhIL-6, demonstrated a significant increase in LI, one of these was first observed in the second **treatment** cycle. A significant decrease was seen in two patients receiving 2.5 micrograms/kg and 5 micrograms/kg respectively. Immunophenotypic assessment demonstrated that rhIL-6 increased the expression of CD20 in all **CLL** patients with a reversal after cessation of rhIL-6. We conclude that rhIL-6, in the dosage and schedule used in this study, did not increase the proportion of the cells in S-phase and that the growth stimulatory effects of rhIL-6 in **CLL** in vivo probably are insignificant. However, the role of rhIL-6 in **CLL** as inducer of increased CD20 expression prior to **anti-CD20** antibody **treatment** remains to be determined.

L10 ANSWER 7 OF 17 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000057628 MEDLINE
DOCUMENT NUMBER: 20057628
TITLE: Tumor lysis syndrome occurring after the **administration** of rituximab in lymphoproliferative disorders: high-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia.
AUTHOR: Yang H; Rosove M H; Figlin R A
CORPORATE SOURCE: The Division of Hematology-Oncology, Department of Medicine, University of California, Los Angeles 90095, USA.. hhyang@pol.net
SOURCE: AMERICAN JOURNAL OF HEMATOLOGY, (1999 Dec) 62 (4) 247-50.
Journal code: 3H4. ISSN: 0361-8609.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200003
ENTRY WEEK: 20000302
AB Rituximab, an **anti-CD20** antibody, has been recently approved for the **treatment** of low-grade or follicular non-Hodgkin's lymphoma (NHL). Because of its relatively benign side effect profile, it has been considered a nontoxic alternative to chemotherapy. Recently, however, tumor lysis syndrome (TLS) resulting from rituximab has been reported in a patient with chronic lymphocytic **leukemia** (**CLL**). We herein present two cases of rituximab-induced TLS. The first case occurred in a patient with high-grade NHL, while the second case occurred in a patient with **CLL**. We also present a summary of the literature regarding TLS induced by immunotherapies. Copyright 1999 Wiley-Liss, Inc.

L10 ANSWER 8 OF 17 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:348053 BIOSIS
DOCUMENT NUMBER: PREV199900348053
TITLE: Low- versus high-dose radioimmunotherapy in acute lymphatic leukemia, non-Hodgkin's lymphoma (NHL) or macroglobulinemia.
AUTHOR(S): Behr, T. M. (1); Woermann, B.; Gramatzki, M.; Riggert, J.; Griesinger, F.; Sharkey, R. M.; Kolb, H. J.; Hiddemann, W.; Goldenberg, D. M.; Becker, W.
CORPORATE SOURCE: (1) Georg-August-University of Goettingen, Goettingen Germany
SOURCE: Journal of Nuclear Medicine, (May, 1999) Vol. 40, No. 5 SUPPL., pp. 222P-223P.
Meeting Info.: 46th Annual Meeting of the Society of Nuclear Medicine Los Angeles, California, USA June 6-10, 1999 Society of Nuclear Medicine
. ISSN: 0161-5505.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 9 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999345510 EMBASE
TITLE: Chimeric monoclonal **anti-CD20** antibody (rituximab) - An effective **treatment** for a patient with relapsing hairy cell **leukaemia**.
AUTHOR: Hagberg H.
CORPORATE SOURCE: Dr. H. Hagberg, Department of Oncology, Akademiska Sjukhuset, 75185 Uppsala, Sweden
SOURCE: Medical Oncology, (1999) 16/3 (221-222).
Refs: 2

ISSN: 0736-0118 CODEN: MONCEZ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A case story is presented, describing a 46 y old man, with a relapsing hairy cell **leukaemia**. After **treatment** with monoclonal **anti CD-20** antibodies (rituximab) 375 mg/week, four times, a complete remission was obtained which has lasted > 9 months. The rituximab **treatment** produced a better remission than earlier **treatments** with alpha-interferon and chlorodeoxyadenosine. In addition, in contrast to other **treatments**, no initial worsening of the pancytopenia was observed.

L10 ANSWER 10 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999334939 EMBASE
TITLE: Monoclonal antibodies in cancer treatment: A review of recent progress.
AUTHOR: Alpaugh K.; Von Mehren M.
CORPORATE SOURCE: Dr. K. Alpaugh, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111, United States. RK-Alpaugh@fccc.edu
SOURCE: BioDrugs, (1999) 12/3 (209-236).
Refs: 151
ISSN: 1173-8804 CODEN: BIDRF4
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Research advances and promising clinical outcomes with immunotherapeutics has led to a resurgence of incorporating monoclonal antibodies in cancer **treatment**. Unconjugated, conjugated and multi-target constructs are emerging as a conventional form of **therapy** along with the classical trio of surgery, radiation and chemotherapy. The recent major accomplishments in monoclonals include: first, the development of human and chimeric structures negating the induction of humoral responses to murine counterparts which limited use; second, protein engineering has improved the affinity and specificity of the antibody to its target; third, technics have been designed to select

monoclonal antibodies imparting a biological consequence (function) following binding; and, lastly, recombinant proteins are being created with multiple epitopic specificities and/or fusion with other biologically active proteins such as toxins and cytokines/growth factors. Clinical efficacy in the **treatment** of **haematological malignancies** has secured a role for monoclonals in routine **treatment**. Evidence of clinical responses in patients with metastatic solid tumours is leading to the next generation of trials in the adjuvant setting. This paper presents an overview of the clinical experience with monoclonal antibodies in cancer **treatment** over the past 5 years. Our aim is to highlight the successes and advances, as well as noting limitations of antibody **therapeutics**. The advances seen support a continued effort to optimise the creation, selection and use of immunotherapeutics in the battle against cancer.

L10 ANSWER 11 OF 17 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000001899 MEDLINE
DOCUMENT NUMBER: 20001899
TITLE: Rituximab (**anti-CD20** monoclonal antibody) **administration** in a young patient with resistant B-prolymphocytic leukemia.
AUTHOR: Vartholomatos G; Tsiara S; Christou L; Panteli A; Kaiafas P; Bourantas K L
CORPORATE SOURCE: Hematology Department, Medical School of Ioannina, Ioannina University, Greece.
SOURCE: ACTA HAEMATOLOGICA, (1999) 102 (2) 94-8. Journal code: 0S8. ISSN: 0001-5792.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200002
ENTRY WEEK: 20000204
AB Following the **administration** of the human **anti-CD20** monoclonal antibody IDEC-C2B8 (rituximab), a 31-year-old woman with B-prolymphocytic **leukemia**, who had been resistant to CHOP, fludarabine, pentostatin and 2-CdA, achieved complete remission. Rituximab was **administered** intravenously once a week for 4 weeks. The patient only had mild but tolerable side effects during the first cycle of **therapy**. She remains in complete remission 8 months following the discontinuation of **treatment**.

L10 ANSWER 12 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999306600 EMBASE
TITLE: An overview of monoclonal antibody therapy of cancer.
AUTHOR: Weiner L.M.

CORPORATE SOURCE: Dr. L.M. Weiner, Department of Medical Oncology, Fox Chase Cancer Center, 7701 Burholme Ave, Philadelphia, PA 19111, United States
SOURCE: Seminars in Oncology, (1999) 26/4 SUPPL. 12 (41-50).
Refs: 43
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Monoclonal antibody-based **therapeutics** are beginning to realize the promise that was predicted with the advent of the core technology more than 20 years ago. Antibody-based **therapeutics** targeting tumor cell surface antigens such as B-cell idiotypes, CD20 on malignant B cells, CD33 on **leukemic** blasts, and HER2/neu on breast cancer cells have shown efficacy in clinical trials. Multiple antibody-based strategies have shown promising efficacy in recent clinical trials. Unconjugated immunoglobulins directed against CD20 induce partial and complete responses in up to 50% of patients with advanced, indolent non-Hodgkin's lymphoma. When such antibodies are conjugated to appropriate radionuclides and **administered** in **therapeutic** doses, the proportions of complete and overall responses increase considerably. Conjugates composed of anti-CD33 antibodies and the chemotherapy agent, calicheamicin, show promising activity in patients with relapsed or refractory acute myelogenous **leukemia**. **Treatment** of patients with advanced breast cancer using the anti-HER2/neu antibody trastuzumab (Herceptin; Genentech, San Francisco) leads to objective responses in some patients whose tumors overexpress the HER2/neu oncoprotein. These exciting results justify recent enthusiasm for continued efforts to refine existing approaches and to develop new antibody-based strategies to **treat** human malignancy.

L10 ANSWER 13 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998374824 EMBASE
TITLE: Monoclonal antibody-based **therapies** for **hematologic malignancies**.
AUTHOR: Multani P.S.; Grossbard M.L.
CORPORATE SOURCE: Dr. M.L. Grossbard, Cox 2, Massachusetts General Hospital, 100 Blossom St., Boston, MA 02114, United States. grossbard.michael@mgh.harvard.edu
SOURCE: Journal of Clinical Oncology, (1998) 16/11 (3691-3710).
Refs: 217
ISSN: 0732-183X CODEN: JCONDN

COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose: To review recent advances in the development and clinical roles of monoclonal antibody (MoAb)-based **therapies** in the **treatment** of **hematologic malignancies**.
Design: A search of MEDLINE and CANCERLIT was conducted to identify relevant publications. The bibliographies of these references also were used to identify articles and abstracts. These references were then reviewed. Results: In the two decades since the first patient was **treated** with MoAb **therapy**, there have been significant advances in the biology, pharmacology, and clinical application of MoAb-based **therapies**. Three distinct fields of research have emerged: unconjugated MoAbs, immunotoxin-conjugated MoAbs (ITs), and radionuclide-conjugated MoAbs (RICs). The unconjugated MoAbs are less toxic but depend on host mechanisms to mediate cytotoxicity. The ITs carry a potent toxin, although at the cost of a narrow **therapeutic** index that may limit clinical use. The RICs offer significant potency, even in refractory disease, but their complexity may limit their use to large cancer centers. The current challenges in the development of MoAb- based **therapies** are to identify the proper target antigens, contend with bulk disease in which penetration may be limited, and choose the optimal clinical settings for their use, such as the minimal residual disease state or in combination with conventional chemotherapy. Conclusion: Although significant research is still needed, MoAb-based **therapies** promise to offer new options for the **treatment** of patients with **hematologic malignancies**.

L10 ANSWER 14 OF 17 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998430961 MEDLINE
DOCUMENT NUMBER: 98430961
TITLE: Rapid tumor lysis in a patient with B-cell chronic lymphocytic **leukemia** and lymphocytosis **treated** with an **anti-CD20** monoclonal antibody (IDEC-C2B8, rituximab).
AUTHOR: Jensen M; Winkler U; Manzke O; Diehl V; Engert A
CORPORATE SOURCE: Department I for Internal Medicine, University of Cologne, Koln, Germany.
SOURCE: ANNALS OF HEMATOLOGY, (1998 Jul-Aug) 77 (1-2) 89-91. Journal code: A2P. ISSN: 0939-5555.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
Searcher : Shears 308-4994

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199812
ENTRY WEEK: 19981204
AB In this report we present a patient with B-cell chronic lymphocytic leukemia who developed an acute tumor lysis syndrome after **administration** of the human **anti-CD20** antibody IDEC-C2B8 (RITUXIMAB) in standard dose of 375 mg/m2. IDEC-C2B8 has been demonstrated to have only mild and tolerable side effects in patients with follicular lymphoma. In these trials patients with lymphocytosis >5000/microl were excluded. Physicians must be aware of this hitherto unreported phenomenon in patients with high CD20-positive blood counts.

L10 ANSWER 15 OF 17 TOXLINE
ACCESSION NUMBER: 1999:107151 TOXLINE
DOCUMENT NUMBER: IPA-99-1175232
TITLE: Immunotherapeutic approaches to treatment of B-cell neoplasms: focus on unconjugated antibodies.
AUTHOR: Ford S M; Donegan S E
CORPORATE SOURCE: Oncol. Pharm. Services, Eisenhower Army Med. Ctr., Ft. Gordon, GA, USA.
SOURCE: Highlights Oncol. Pract, (1998). Vol. 16, No. 2, pp. 40-50 (REF 64).
ISSN: 1088-7164.
FILE SEGMENT: IPA
LANGUAGE: English
OTHER SOURCE: IPA 36-1175232
ENTRY MONTH: 199909
AB IPA COPYRIGHT: ASHP An overview of the use of immunotherapy in 2 B-cell neoplasms, low-grade non-Hodgkin's lymphoma (NHL), and chronic lymphocytic **leukemia** (**CLL**) is presented, and current **treatment** strategies for NHL and **CLL** , the rationale behind immunotherapy for these neoplasms, and the use of rituximab (IDEC-C2B8; **anti-CD20**; **Rituxan**), an unconjugated monoclonal antibody (MoAb), in NHL, including the mechanism of action, pharmacokinetics, clinical studies, adverse effects, and dosage and **administration** of this agent, Campath-1H, another MoAb, in NHL and **CLL**, and anti-idiotype neoplasm vaccines in NHL are considered.

L10 ANSWER 16 OF 17 TOXLINE
ACCESSION NUMBER: 1995:206899 TOXLINE
DOCUMENT NUMBER: CRISP-95-M09390-02
TITLE: HUMANIZATION OF IMMUNOTOXINS.
AUTHOR: RYBAK S M
CORPORATE SOURCE: NCI, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, DIVISION OF

CANCER TREATMENT.
CONTRACT NUMBER: Z01CM09390-02
SOURCE: (1994). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199507

AB RPROJ/CRISP The goal of this work is to use human RNases and homologous RNases from other species instead of toxic plant and bacterial proteins in the construction of immunotoxins. Two of the major problems with the clinical use of immunotoxins is the toxicity and immunogenicity of the toxins. The use of human RNases that acquire toxicity by targeting addresses these problems. Chemical conjugates of antibodies to the human transferrin receptor conjugated to bovine RNase A inhibited the growth of human glioma cells in an animal model as well as a ricin-A chain conjugate constructed with the same **antibody**. The IC50 of a recombinant **chimeric** mouse/**human** **antibody** to the **human** transferrin receptor fused to the gene for human angiogenin RNase to kill human **leukemia** cells was 5 X 10(-11) M. This compared very well with the in vitro potency of classical immunotoxins. A single chain antibody constructed from the chimeric anti-transferrin receptor antibody was fused to the gene for human eosinophil RNase and expressed in bacteria. This antibody enzyme construct specifically bound to its target cells, expressed specific RNase activity and killed human tumor cells with an IC50 of 5 X 10(-10) M. A homologous RNase (Onconase) from frog oocytes has inherent anti-tumor properties and is in clinical trials as an anti-cancer agent. Onconase has been **administered** to humans on a weekly basis for up to six months without causing immunological problems or serious toxicities, presumably because of its homology to human plasma RNases. The specificity of Onconase as an anticancer agent can be improved by targeting and to this end the gene has been cloned from Rana pipiens genomic DNA. Onconase has been demonstrated to have specific activity against HIV-1 and these results were confirmed in the NCI AIDS screen. Thus, the potent targeted cytotoxicity of these new reagents can also be directed to MDS **therapies**.

L10 ANSWER 17 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91093098 EMBASE
DOCUMENT NUMBER: 1991093098
TITLE: Myeloablative therapy with autologous bone marrow transplantation as consolidation of remission in patients with follicular lymphoma.
AUTHOR: Rohatiner A.Z.S.; Price C.G.A.; Arnott S.; Norton A.; Evans M.L.; Cotter F.; Dorey E.; Davis C.L.; Clark

Searcher : Shears 308-4994

P.; Sterlini J.; Lim J.; Horton M.; Lister T.A.
CORPORATE SOURCE: ICRF Dept. of Medical Oncology, St. Bartholomew's Hospital, London EC1A 7BE, United Kingdom
SOURCE: Annals of Oncology, (1991) 2/SUPPL. 2 (147-150).
ISSN: 0923-7534 CODEN: ANONE2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A study has been in progress since June 1985 to evaluate the use of myeloablative **therapy** (cyclophosphamide [60 mg/kg x 2] and total body irradiation [200 cGy x 6]) followed by reinfusion of autologous bone marrow in patients in second or subsequent remission of B-cell non-Hodgkin's lymphoma. The marrow mononuclear cell fraction is being **treated** in vitro with three cycles of the monoclonal antibody **anti-CD20** (anti-B1, Coulter Immunology) and baby rabbit complement (Pel-Freez). Thirty-eight patients with follicular lymphoma (age range 29-61 years, median 43) have been **treated** to date. At the time of **treatment**, 28 patients were in second remission, 7 were in third, and 3 were in more than third remission. Twenty-three patients were in complete remission, 15 had residual disease (7 had lymph nodes < 2cm diameter, 4 had < 10% bone marrow infiltration, 1 had involvement of lymph nodes and bone marrow, and 3 had involvement at other sites). Of the 38 study patients, 32 are alive; 6 have died, 4 in remission. Two of the deaths were **treatment** related: 1 resulted from cerebral haemorrhage at 29 days; 1 resulted from systemic fungal infection at three months). One patient died from secondary acute myelogenous **leukaemia** at four years, and another from an unrelated cause. Two patients died following relapse. The median time to engraftment was 28 days (range 15-45 days) for neutrophils > 0.5 x 109/L and 28 days (range 15-46 days) for platelets > 20 x 109/L. Twenty-six patients continue in remission between one month and five years (median follow-up 22 months); 8 have relapsed, 2 with transformation to high-grade histology. In the context of the natural history of follicular lymphoma these results are preliminary but encouraging. It remains to be established whether such intensive **therapy** is curative.

FILE 'CAPLUS' ENTERED AT 11:38:17 ON 01 FEB 2000
L11 15 SEA ABB=ON PLU=ON L2 AND (ANTICD20 OR ANTICD 20 OR ANTI(W)(CD20 OR CD 20) OR L1 OR RITUXAN)
L12 33 SEA ABB=ON PLU=ON L2 AND ((CHIMER?(5A)ANTIBOD?)(5A)HUMAN?)
L13 2 SEA ABB=ON PLU=ON L12 AND ADMIN?
Searcher : Shears 308-4994

L14 9 SEA ABB=ON PLU=ON (L11 OR L13) NOT L6

L14 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:14234 CAPLUS
DOCUMENT NUMBER: 132:48782
TITLE: Tumor lysis syndrome occurring after the administration of rituximab in lymphoproliferative disorders: high-grade non-Hodgkin's lymphoma and chronic lymphocytic **leukemia**
AUTHOR(S): Yang, Honghao; Rosove, Michael H.; Figlin, Robert A.
CORPORATE SOURCE: The Division of Hematology-Oncology, Department of Medicine, University of California, Los Angeles, CA, 90095, USA
SOURCE: Am. J. Hematol. (1999), 62(4), 247-250
CODEN: AJHEDD; ISSN: 0361-8609
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rituximab, an **anti-CD20** antibody, has been recently approved for the treatment of low-grade or follicular non-Hodgkin's lymphoma (NHL). Because of its relatively benign side effect profile, it has been considered a nontoxic alternative to chemotherapy. Recently, however, tumor lysis syndrome (TLS) resulting from rituximab has been reported in a patient with chronic lymphocytic **leukemia** (**CLL**). We herein present two cases of rituximab-induced TLS. The first case occurred in a patient with high-grade NHL, while the second case occurred in a patient with CLL. We also present a summary of the literature regarding TLS induced by immunotherapies.
IT **174722-31-7**, Rituximab
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rituximab-induced tumor lysis syndrome in humans with high-grade non-Hodgkin's lymphoma or chronic lymphocytic **leukemia**)

L14 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:740269 CAPLUS
DOCUMENT NUMBER: 131:319707
TITLE: Low- versus high-dose radioimmunotherapy with humanized anti-CD22 or chimeric **anti-CD20** antibodies in a broad spectrum of B cell-associated malignancies
AUTHOR(S): Behr, Thomas M.; Wormann, Bernhard; Gramatzki, Martin; Riggert, Joachim; Gratz, Stefan; Behe, Martin; Griesinger, Frank; Sharkey, Robert M.; Kolb, Hans-J.; Hiddemann, Wolfgang; Goldenberg, David M.; Becker, Wolfgang

CORPORATE SOURCE: Departments of Nuclear Medicine, Georg-August-University of Gottingen, Gottingen, D-37075, Germany
SOURCE: Clin. Cancer Res. (1999), 5(10, Suppl.), 3304s-3314s
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Both CD22 and CD20 have been used successfully as target mols. for radioimmunotherapy (RAIT) of low-grade B cell non-Hodgkin's lymphoma. Because both CD20 and CD22 are highly expressed relatively early in the course of B cell maturation, and because its expression is maintained up to relatively mature stages, we studied the potential of the humanized anti-CD22 antibody, hLL2, as well as of the chimeric **anti-CD20** (chCD20) antibody, rituximab (IDEC-C2B8), for low- or high-dose (myeloablative) RAIT of a broad range of B cell-assocd. **hematol. malignancies**. A total of 10 patients with chemorefractory malignant neoplasms of B cell origin were studied with diagnostic (n = 5) and/or potentially therapeutic doses (n = 9) of hLL2 (n = 4; 0.5 mg/kg, 8-315 mCi of 131I) or chCD20 (n = 5; 2.5 mg/kg, 15-495 mCi of 131I). The diagnostic doses were given to establish the patients' eligibility for RAIT and to est. the individual radiation dosimetry. One patient suffered of Waldenstrom's macroglobulinemia, eight patients had low- (n = 4), intermediate- (n = 2) or high- (n = 2) grade non-Hodgkin's lymphoma, and one patient had a chemore-factory acute lymphatic **leukemia**, after having failed five heterologous bone marrow or stem cell transplantations. Three of these 10 patients were scheduled for treatment with conventional (30-63 mCi, cumulated doses of up to 90 mCi of 131I) and 7 with potentially myeloablative (225-495 mCi of 131I) activities of 131I-labeled hLL2 or chCD20 (0.5 and 2.5 mg/kg, resp.); homologous (n = 6) or heterologous (n = 1) stem cell support was provided in these cases. Good tumor targeting was obsd. in all diagnostic as well as posttherapeutic scans of all patients. In myeloablative therapies, the therapeutic activities were calcd. based on the diagnostic radiation dosimetry, aiming at lung and kidney doses .ltoreq. 20Gy. Stem cells were reinfused when the whole-body activity retention fell below 20 mCi. In eight assessable patients, five had complete remissions, two experienced partial remissions (corresponding to an overall response rate of 87%), and one (low-dose) patient had progressive disease despite therapy. In the five assessable, actually stem-cell grafted patients, the complete response rate was 100%. Both CD20 and CD22 seem to be suitable target mols. for high-dose RAIT in a broad spectrum of **hematol. malignancies** of B cell origin with a broad range of maturation stages (from acute lymphatic **leukemia** to Waldenstrom's macroglobulinemia). The better

therapeutic outcome of patients undergoing high-dose, myeloablative RAIT favors this treatment concept over conventional, low-dose regimens.

IT **174722-31-7**, Rituximab
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low- vs. high-dose radioimmunotherapy with humanized anti-CD22 or chimeric **anti-CD20** antibodies in broad spectrum of B cell-assocd. malignancies)

L14 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:680426 CAPLUS
DOCUMENT NUMBER: 131:309650
TITLE: Rituximab (**anti-CD20** monoclonal antibody) administration in a young patient with resistant B-prolymphocytic **leukemia**
AUTHOR(S): Vartholomatos, G.; Tsiara, S.; Christou, L.; Panteli, A.; Kaiafas, P.; Bourantas, K. L.
CORPORATE SOURCE: Hematology Department, Medical School, Ioannina Univ., Ioannina, GR-45500, Greece
SOURCE: Acta Haematol. (1999), 102(2), 94-98
CODEN: ACHAAH; ISSN: 0001-5792
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Following the administration of the human **anti-CD20** monoclonal antibody IDEC-C2B8 (rituximab), a 31-yr old woman with B-prolymphocytic **leukemia**, who had been resistant to CHOP, fludarabine, pentostatin, and 2-CdA, achieved complete remission. Rituximab was administered i.v. once a week for 4 wk. The patient only had mild but tolerable side effects during the 1st cycle of therapy. She remains in complete remission 8 mo following the discontinuation of treatment.

IT **174722-31-7**, Rituximab
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rituximab (**anti-CD20** monoclonal antibody) administration in a young patient with resistant B-prolymphocytic **leukemia**)

L14 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:352921 CAPLUS
DOCUMENT NUMBER: 131:169216
TITLE: Cytocidal activity of PBL, LAK, and IDEC-C2B8 and expression of HLA class 1, ICAM-1, and CD20 in vincristine-resistant hematologic cell lines
AUTHOR(S): Hirose, Masao; Hamano, Shuichi; Tobinai, Kensei; Kuroda, Yasuhiro
CORPORATE SOURCE: Division of Transfusion Medicine, School of

Dentistry, The University of Tokushima, Tokushima, Japan
SOURCE: J. Immunother. (1999), 22(3), 237-244
CODEN: JOIMF8; ISSN: 1053-8550
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study was designed to det. whether the cytocidal activity of immunotherapy such as cytotoxic peripheral blood lymphocytes (PBL), lymphokine-activated killer (LAK) cells, and chimeric **anti-CD20** mouse/human monoclonal antibody, IDEC-C2B8, overcome vincristine (VCR) resistance in cultured cell lines derived from human **leukemia**/lymphoma. In addn., the relation between the susceptibility to these immunotherapies and the expression levels of HLA class 1 and ICAM-1 as well as CD20 on the cell surface was analyzed. Three of six VCR-resistant cell lines were less susceptible to PBL cytotoxicity compared with wild-type cells, whereas the susceptibility was kept in the other three VCR-resistant cell lines. Four of six VCR-resistant cell lines were less susceptible to LAK activity and the other two cell lines were as sensitive to LAK cells as their wild-type counterparts. There was no correlation between the susceptibility for PBL cytotoxicity and the expression of HLA class 1 in both wild and VCR-resistant cells. In contrast, ICAM-1 in the two cell lines that showed decreased susceptibility for LAK cytotoxicity disappeared, although that in one cell line increased. IDEC-C2B8 was effective only against B-cell lines expressing CD20. One cell line in which the expression of CD20 increased was nearly six times more sensitive to IDEC-C2B8 than wild type. Thus, we concluded that the resistance to VCR in some tumor cell lines is assocd. with modified susceptibility for immunotherapies by the different expression of target mols. from those of wild-type counterparts.

L14 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:129923 CAPLUS
DOCUMENT NUMBER: 130:250947
TITLE: IDEC-C2B8 **anti-CD20** (rituximab) immunotherapy in patients with low-grade non-Hodgkin's lymphoma and lymphoproliferative disorders: evaluation of response on 48 patients
AUTHOR(S): Nguyen, D. T.; Amess, J. A.; Doughty, H.; Hendry, L.; Diamond, L. W.
CORPORATE SOURCE: Department of Haematology, Laboratory Division, Bartholomew's Hospital, London, UK
SOURCE: Eur. J. Haematol. (1999), 62(2), 76-82
CODEN: EJHAEC; ISSN: 0902-4441
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study focused on the efficacy of IDEC-C2B8 (chimeric **anti-CD20**) immunotherapy relative to specific subtypes of low-grade lymphoproliferative disorders/non-Hodgkin's lymphomas (LPD/NHL). Forty-eight patients with resistant or relapsed disease completed the IDEC-C2B8 infusion schedule of 375 mg/m2/wk .times. 4 wk. The LPD/NHL subtypes included: (a) follicular center cell lymphoma (FCC) in 22 patients; (b) mantle cell lymphoma (MCL) in 10; (c) 1 diffuse large cell lymphoma (DLCL); and (d) the category of small lymphocytic lymphoma/chronic lymphocytic **leukemia** (SLL/**CLL**) and related disorders in 15 patients. No patient obtained a complete remission. Ten patients (21%) achieved partial remission: 6 FCC, 2 MCL, 1 DLCL and 1 patient from the SLL/CLL group. Twenty-eight patients had stable disease and 10 progressed during immunotherapy. In patients with **CLL** and MCL in **leukemic** phase, there was no correlation between the marked decrease in circulating neoplastic cells following antibody infusions and amelioration of the tumor burden. The results suggest that the subtype of LPD/NHL and the intensity of CD20 on the tumor cells influence the effectiveness of IDEC-C2B8. The antibody was most efficacious against FCC lymphoma. The efficacy (at the dose schedule of 375 mg/m2/wk .times. 4) against MCL and SLL/CLL appeared to be limited, however.

IT **174722-31-7**, Rituximab
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(IDEC-C2B8 **anti-CD20** (rituximab) immunotherapy in humans with low-grade non-Hodgkin's lymphoma and lymphoproliferative disorders)

L14 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:272384 CAPLUS
DOCUMENT NUMBER: 129:93687
TITLE: FMC7 antigen expression on normal and malignant B-cells can be predicted by expression of CD20
AUTHOR(S): Hubl, Wolfgang; Iturraspe, Jose; Braylan, Raul C.
CORPORATE SOURCE: Department of Pathology, University of Florida College of Medicine, Gainesville, FL, 32610-0275, USA
SOURCE: Cytometry (1998), 34(2), 71-74
CODEN: CYTODQ; ISSN: 0196-4763
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Most antibody panels proposed for flow cytometric immunophenotyping of non-Hodgkin's lymphomas and chronic lymphoid **leukemias** include **anti-CD20** and FMC7 antibodies. As in

our experience, reactivity of B-cells with these antibodies seemed to be correlated, we evaluated whether the simultaneous use of **anti-CD20** and FMC7 antibodies is justified. Using flow cytometry, we measured the binding of these 2 antibodies to the B-cells of 67 bone marrow aspirates, 31 lymph node biopsies, 18 peripheral blood specimens, and 12 tissue samples from other locations. The diagnoses included 50 cases without overt abnormalities, 5 reactive lymphadenopathies, 56 lymphomas and chronic lymphoid neoplasias, and 17 cases with other malignancies. Although CD20 expression was consistently higher, we obsd. a significant and strong correlation between CD20 and FMC7 antigen expression on B-lymphocytes, irresp. of the nature of the sample or disease ($r = 0.910$; $P < 0.001$). Moreover, FMC7 antigen expression on B-cells could be predicted by CD20 expression with a sensitivity of 96%, a specificity of 94% and an efficiency of 96%. Our results show that although differing in intensity, expression of CD20 on B-cells closely parallels that of FMC7 antigen. We, therefore, conclude that little addnl. information is revealed by using FMC7 in immunophenotyping of non-Hodgkin's lymphomas or chronic lymphoid **leukemias** if intensity of CD20 expression is taken into consideration.

L14 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1991:18953 CAPLUS
DOCUMENT NUMBER: 114:18953
TITLE: Gene expression elements and the production of **chimeric** mouse-**human antibodies**
INVENTOR(S): Better, Marc D.; Horwitz, Arnold H.; Robinson, Randy R.; Lei, Shau Ping; Chang, Changtung Paul
PATENT ASSIGNEE(S): International Genetic Engineering, Inc., USA
SOURCE: Eur. Pat. Appl., 123 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 364096	A2	19900418	EP 1989-309048	19890906
EP 364096	A3	19920805		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
WO 9002569	A1	19900322	WO 1989-US3852	19890906
W: AU, BR, DK, FI, JP, KR, NO, US, US, US, US, US, US				
AU 8944021	A1	19900402	AU 1989-44021	19890906
AU 643189	B2	19931111		
EP 967277	A2	19991229	EP 1999-202598	19890906
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				

Searcher : Shears 308-4994

AU 9057547	A1	19901220	AU 1990-57547	19900618
AU 627591	B2	19920827		
EP 404003	A2	19901227	EP 1990-111426	19900618
EP 404003	A3	19911016		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2019323	AA	19901219	CA 1990-2019323	19900619
JP 03280884	A2	19911211	JP 1990-162545	19900619
US 5576184	A	19961119	US 1994-364001	19941227
US 5843685	A	19981201	US 1995-466034	19950606
PRIORITY APPLN. INFO.:			US 1988-240624	19880906
			US 1988-241744	19880908
			US 1988-243739	19880913
			US 1988-253002	19881004
			US 1989-367641	19890619
			US 1989-382768	19890721
			EP 1989-309048	19890906
			WO 1989-US3852	19890906
			US 1991-659401	19910506
			US 1994-364001	19941227

AB Chimeric antibodies of variable regions of a mouse monoclonal antibody (Mab) against human tumor cells and const. region of human Ig are manufd. in a no. of hosts using appropriate expression cassettes. **Administered** in **human**, the **chimeric antibodies** may lower the immune response, and prolong survival in the circulation through reduced clearance. Expression vectors pING2207 and pING2225 encoding chimeric light chain and chimeric heavy chain, resp., of variable region of mouse B38.1 Mab against human breast carcinoma and human Ig const. region were constructed and transformed into Sp2/0 cells. The Sp2/0 transformants produced and secreted chimeric antibody ING-1 10-15 .mu.g/mL. The chimeric antibody ING-1, in a binding inhibition assay, showed identical properties to those of mouse B38.1 Mab. In complement-dependent cytolysis (CDC) or antibody-dependent cellular cytotoxicity (ADCC) assays using human colon carcinoma HT-29 cells as target cells, it was efficient at mediating ADCC lysis of the target cells and mediated 16% lysis of the target cells by CDS; mouse Mab B38.1 MAb was inactive in both assays. Prepn. of the chimeric antibodies in Saccharomyces cerevisiae and Escherichia coli was also demonstrated.

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ACCESSION NUMBER:	1987:174317 CAPLUS
DOCUMENT NUMBER:	106:174317
TITLE:	Value of monoclonal anti-CD22 (p135) antibodies for the detection of normal and neoplastic B lymphoid cells
AUTHOR(S):	Mason, D. Y.; Stein, H.; Gerdes, J.; Pulford, K. A. F.; Ralfkiaer, E.; Falini, B.; Erber, W. N.; Micklem, K.; Gatter, K. C.

Searcher : Shears 308-4994

CORPORATE SOURCE: Nuffield Dep. Pathol., John Radcliffe Hosp., Oxford, UK
SOURCE: Blood (1987), 69(3), 836-40
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two monoclonal antibodies (To15 and 4KB128) specific for the B cell-assocd. CD22 antigen (135,000 mol. wt.) are described. On immunoenzymic anal. of cryostat tissue sections, these antibodies strongly label both mantle zone and germinal center B lymphoid cells in secondary lymphoid follicles (and also scattered extrafollicular lymphoid cells) but are unreactive with other cell types (with the exception of weak reactivity with some epithelioid histiocytes). These reactions differ from those of monoclonal antibodies B1 and B2 (**anti-CD20** and CD21) but are similar to those of the pan-B antibody B4 (anti-CD19). One of the anti-CD22 antibodies (To15) has been tested extensively by immunoenzymic labeling on >350 neoplastic lymphoid and hematol. samples. The CD22 antigen was found in tissue sections in most B cell-derived neoplasms, the major exceptions being myeloma (all cases neg.) and a small proportion of high-grade lymphoma (6% of cases neg.). In cell smears, the antigen could be found on neoplastic cells in most B cell lymphoproliferative disorders, including common acute lymphoblastic **leukemia** (90% pos.) and B cell chronic lymphocytic **leukemia** (89% pos.). Thus, anti-CD22 antibodies are of value for identification of human B cell lymphoproliferative disorders (esp. when used in conjunction with anti-CD19 antibodies). Previous reports that the CD22 antigen is absent from many B cell neoplasms are probably due to its being expressed within the cytoplasm of immature B cells rather than on their surface.

L14 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1987:117719 CAPLUS
DOCUMENT NUMBER: 106:117719
TITLE: Augmentation of normal and malignant B cell proliferation by monoclonal antibody to the B cell-specific antigen BP50 (CDW40)
AUTHOR(S): Ledbetter, Jeffrey A.; Shu, Geraldine; Gallagher, Mary; Clark, Edward A.
CORPORATE SOURCE: Oncogen Corp., Seattle, WA, 98121, USA
SOURCE: J. Immunol. (1987), 138(3), 788-94
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A 50,000 dalton polypeptide Bp50 (CDw40) was recently described that is expressed on human B cells and plays a role in regulating B cell proliferation. The authors addnl. characterize the functional signal given by antibody binding to Bp50 on both normal and malignant B cells. A monoclonal anti-Bp50 antibody augmented the